Emerging cures for cancer: peptides from scorpion and spider venom

Jiayi He[1, †, *], Yedong Xue[2, †]

[1]Benenden school, Kent, United Kingdom

[2]Guanghua Cambridge International School, Shanghai, China

[†]These authors contributed equally to this paper

*Corresponding author: 15000440237@xs.hnit.edu.cn

Abstract. Animal toxins have shown applicability in treatments of various diseases, here some investigations of scorpion and spider venom peptides as cancer treatments have been presented. Scorpion peptides are believed to have antitumor and analgesic effects and may present the potential to be applied in human medicine as a drug for cancer. Similarly, some spider peptides either directly or indirectly are also proved to regulate tumour cell growth and death. Mechanism involved includes promoting cell apoptosis to prevent translocation of cancer cells thus control tumour growth. Such effects make these peptides promising drug candidates for cancer treatment. All five of scorpion venom peptide drugs being approved by FDA for clinical treatment, from which remarkable treating outcomes have been observed when treating cancers. In this paper, general aspects of different scorpion venoms as well as their anticancer mechanism have been thoroughly analysed, from which the successful application of *Buthus martensii* Karsch analgesic peptide in treating carcinoma was elected as the representative case.

Keywords: Scorpion venom, spider venom, peptides, ion channels, breast cancer, BmK AGAP, MDA-MB-231, MCF-7, cancer, antitumor, analgesic, cell apoptosis.

1. Introduction

By number, cancer is amongst the most significant causes of death globally, with a record-breaking number of 10 million deaths in 2020 alone, and statistically accounts for one-sixth of all deaths globally, of which accounts for 2.26 million cases, subsequently the source of over 685 000 deaths in 2020 [1]. Cancer is a disease caused by mutations of certain genes such as tumour suppressor BRCA1/BRCA2 genes and is also a type of malignant tumour. Invasion, uncontrolled growth, and abnormal mass of cells are major properties of cancer. Smoking, infections, occupational exposure to environmental pollutants, malnutrition, and genetic factors are all intimately associated with the development. 'Cancer' is a general terminology for majority of diseases that cause dysfunctional organs or other parts of the body. One of the most noticeable characteristics of such illness is the rapid replication of abnormal body cells at an uncontrollable rate, which invades and metastases into major areas of individuals. Although figuratively speaking, early developments of cancer can be treated and cured at early stages, cancer is still seen as one of the most vicious, unpredictable, and detrimental diseases. It is also worth noting that despite many technological advances in this modern society, there is a severe lack of effective and safe approaches to destroy cancerous cells. However, there are also new directions which suggest the use of natural resources as a solution by minimizing DNA synthesis and metastasis whilst aiding apoptosis to achieve a non-aggressive way of creating a cure through the administration of scorpion and spider venom peptides as a therapeutic drug in clinical treatments.

Cancer is believed to be the result of mutations of bases or genes within the chromosome which also consists of cellular transformations, this often gifts malignant cells some specific characteristics: Firstly, apoptosis and immunosurveillance properties in tissues will be terminated, resulting in the cell's disability to recognize pathogens using the body's immune system and activate natural defence mechanism; Secondly, certain genes coding for ion channel proteins or other expressions may become

misinterpreted or altered, which leads to cancerous cell proliferation (DNA synthesis) at rapid rates; Moreover, angiogenesis(making new blood vessels) is also a significant indicator of the dysfunctional system as its growth factors are often overexpressed in cancer cells, thus inhibition of these genes decreases tumour sizes; Additionally, mass depolarization of cells is a sign of a malfunctional system, the immune cells could even eventually aid the development of cancer by amplifying the sizes of tumours. Lastly, cancer has high mobility and has great potential to metastasize into other parts of the body and invade multiple locations.

It has been universally recognized that ion channels have the role to strengthen mitosis and DNA synthesis, in addition to invasive activities of tumour cells [2]. The expression of the channels has been studied and concluded that overexpressed ion channels is directly related to many different types of cancers, namely glioblastoma and breast cancer. Ion channels have such an active role in pathways of apoptosis to induce cancer cell death in which activation of divalent cations e.g., Ca2+ in addition to monovalent cations such as Na+ and K+ (essential in both cell proliferation and apoptosis) and modulation of ion channels on plasma membranes which could be an effector to the carcinogenic progressions. These channels' mechanisms enhance the progression of malignant cells and DNA synthesis, therefore facilitates the growth of tumours in size. Scorpion venom peptides have been experimentally validated to conclude their function through three named anti-proliferative mechanisms: 1) apoptosis, 2) artificially inhibited progression through the cell cycle and 3) prevention of translation and transcription in DNA replication. To start with, human-induced apoptosis was initially a result of increased expression of Bax gene, which pierces through the mitochondrion membrane to mediate programmed deaths of cancer cells. This cellular process may be one of the most important factors and is targeted in all cancer treatments as any increase in the expression of apoptosis can induce reduced tumour size, thus malignant cells can be successfully eliminated. Furthermore, remodelling of proteins at checkpoints by administration of *Androctonus mauritanicus* venom within the cell cycle has also provided crucial evidence for the anti-proliferative mechanism in colon cancer. Another example is BmK (*Buthus martensii* Karsch), in which replication was terminated at G1 phase during replication by retarding the regulatory protein cyclin D.

Spiders are arthropods with a body length of 1-90mm, which is divided into two main parts: the head and abdomen [3]. Its mouthpart is the main section that secretes venom for killing prey. Most of the spider venom contains peptides, proteins, salts, and small organic molecules [4]. The peptides in spider venom can distort the central nervous system of its prey by interacting with the target receptors or ion channels, and these peptides have a high affinity and specificity to their targets. Due to those factors, spider venom is often studied in research for potential drugs that could be put into use in future.

Several studies have focused on drug development by biotoxins from many different venoms of different species of spiders. Zhang et al. investigated the effect of venom of Lycosa vittate, from which five cell lines were tested to study the anticancer effect of venom from Lycosa vittata. The results show that the IC50 values for human prostatic carcinoma cell line (PC-3) were 31.6±2.5 g/mL. Surprisingly, the venoms exhibited specific cytotoxic ability against all the tested cell lines, and PC-3 was the most susceptible target for all cell lines. These findings suggest that anticancer compounds, particularly agents that target PC-3, can be extracted from this venom.

Scorpion venom (SV) is composed of a variety of peptides differed in functions and lengths, and inorganic compounds as well as free amino acids, which gives SV the ability to block or inhibit the ion channels which are generally overexpressed in cancerous tissues or cells, such as Voltage-gated Sodium Channels (VGSC) [5]. It is believed that SV not only has a huge potential in pluripotent ability in treatments of cancer through clinical drug administration but also indicates the presence of anticancer agents in certain species of scorpion for example Rhopalurus Princeps, stimulating immune system to enhances cancer defence mechanism without triggering adverse effects.

2. Spider Venom

2.1. Enhanced anticancer effect of spider peptide LVTX-9 through fatty acid modification

In a recent study done by Fengjiao Li et al, peptide LVTX-9 from *Lycosa vittata* was isolated to test its toxicity after modified by fatty acids (octadecanoic acid conjugation) [6]. The five lipopeptides produced had an increasing number of carbon atoms from 12 carbons to 20 carbons and an ascending order of hydrophobicity. Researchers have selected the mouse skin melanoma cells (B16-F10 cells) to test the ability of five lipopeptides to kill tumour cells via a Cell Counting Kit 8. It can count the number of live cells with the presence of an electron carrier by the reduction of a water-soluble tetrazolium salt to produce an orange formazan dye. All the lipopeptides in the experiment have demonstrated different cytotoxicity to the B16-F10 cells compared with the unmodified LVTX-9 as presented in figure 1. Among these lipopeptides, LVTX-9-C18 has shown the strongest cytotoxicity in both serum-free and serum-containing conditions, and the cytotoxic ability of LVTX-9-C18 was much higher than the cytotoxic ability shown by LVTX-9 (Figure1).

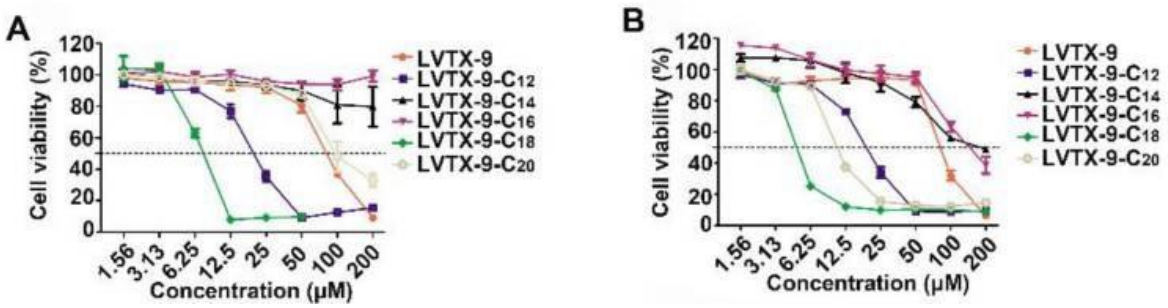

Fig 1. LVTX-9 and five lipopeptides' cytotoxic effects on mouse skin melanoma cells in the media with serum (A) and without serum (B) were assessed using the CCK-8 assay, adapted from ref[6].

Another conclusion drawn in the same study showed the anti-proliferation property of LVTX-9-C18 from colonial formation testing [6]. There were three groups of variables: the control group, 10μM of LVTX-9 and 1μM of LVTX-9-C18. Mouse skin melanoma cells were cultured inside a plate with wells for 36 h, and then the required concentration of LVTX-9 and LVTX-9-C18 were mixed with the cells. After incubated under 37℃ for 7 days, a strong anti-proliferation effect of LVTX-9-C18 (26 ± 2.9) against B16-F10 cells was observed. The colony of B16-F10 cells is significantly lower in the wells containing LVTX-9-C18 than in the control group (51 ± 12.0) and group treated with LVTX-9 (58 ± 11.4) as presented in figure 2. The colony formation of LVTX-9-C18 had a much smaller area, which indicated the efficient anti-proliferation effect of the lipopeptide LVTX-9-C18. However, this leads to a problem of lacking selectivity.

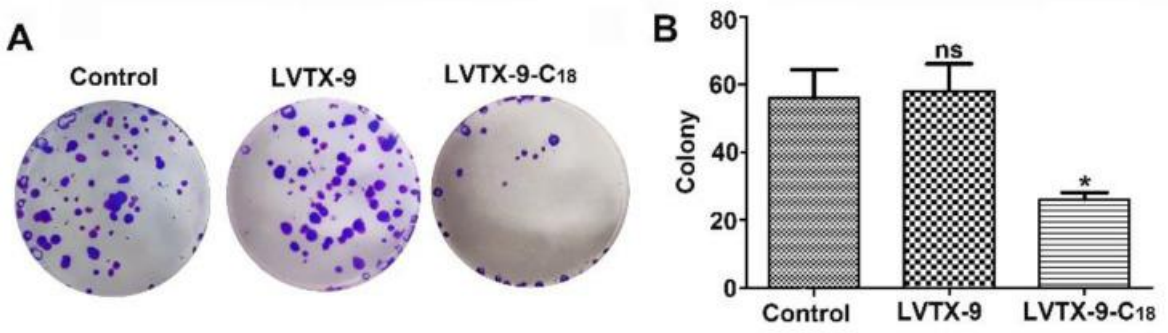

Fig. 2 Effect of LVTX-9 and LVTX-9-C18 on anti-proliferation: (A) By using a colony formation assay, the viability of colony formation in mouse skin melanoma cells mixing with LVTX-9 or LVTX-9-C18 was assessed. (B) Bar chart presenting the colony formation quantitively. Adapted from ref [6].

Fortunately, it was also shown that LVTX-9-C18 has cytotoxicity to the 3D tumour spheroids based on a cytotoxic assay in vitro [6]. As a result, researchers conjecture that LVTX-9-C18 has the

cytotoxic ability to cancer cells in animals. Therefore, it has the potential to be taken into use in future medical treatment of cancer. Moreover, researchers have provided the following explanation for the significant enhancement in cytotoxic activity of LVTX-9-C18 in light of its physical and chemical properties: as LVTX-9 disrupts cancer cell membranes by binding to the membranes via electrostatic interaction, the addition of octadecanoic acid to LVTX-9 can raise its zeta potential, and zeta potential is an electrostatic potential found very close to the surface of particles floating in liquids. Therefore, an increase in zeta potential could improve the peptide's capacity to attach to cancer cell membranes. Additionally, the helical shape and the increased hydrophobicity improved LVTX-9's partitioning and insertion into cancer cell membranes.

2.2. Anticancer effect of spider peptide toxin lycosin-I

Hongwei Shen et al tested the ability of toxin lycosin-I to prevent the migration of malignant cells (PC-3 and DU-145 cells) and promote cell suicide [7]. Lycosin-I at the concentration of 5μM considerably prevent the translocation of those cells but does not affect cell apoptosis or any changes inside cells. However, researchers found that increased doses as 10μM and 20μM both cause cell death resulting from observation of the formation of dead cell bodies and other cellular changes. After 48 hours, a solution for staining called DAPI was added to every well containing cancer cells, and the cells were then examined under a fluorescence microscope. It can be concluded from Figures 3 that the apoptosis of cancer cells positive correlated with the concentration of lycosin-I. Experiments were also carried out in a mouse model. The outcome were the same as observed results of in vitro studies. Besides, the PCA cell migration was inhibited through the STAT3 signalling pathway.

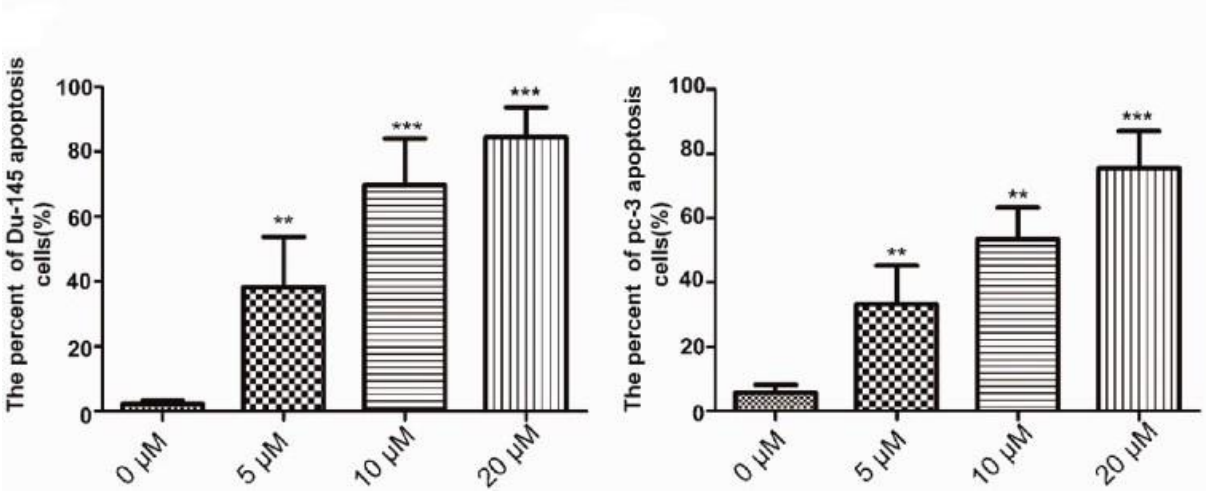

Fig. 3 The apoptotic rates of PCA cells when varied doses of lycosin-I were used. Adapted from ref[7].

Quantitative real-time polymerase chain reaction was utilized to identify modifications in gene expression levels [7]. When 5μM of lycosin-I was added to PCA cells, it was evident that MMP9's mRNA expression was considerably reduced, although other tumour intrusion and translocation genes showed no significant changes. This demonstrates how lycosin-I might prevent cell migration by suppressing MMP9 expression. In the examination of two caspase protein concentrations in PCA cells treated with lycosin-I, researchers found that the expression of two cleaved caspase proteins rose as dose increases. Lycosin-I might activate apoptotic signalling and increase apoptosis of these cancer cells at high concentrations because caspase protein transduces apoptosis signals or directly serves as an effector molecule of apoptosis, causing cytoskeleton disintegration and DNA fragmentation [8].
Fatty acid modification of peptide lycosin-I has also been carried out, from which the five produced peptides were tested in A549 cell lines to validate the cytotoxicity of those lipopeptides in serum-containing and serum-free media [9]. Results have shown that all the modified peptides possessed enhanced cytotoxic effect. More significantly, R-C16 was the most cytotoxic lipopeptide among all the five lipopeptides, and modification enhanced its efficiency by 3-4 times than the original form

lycosin-I. It was observed that R-C16 could destroy the cell membrane of cancer cells to cause apoptosis as have been observed from lactate dehydrogenase leaking assay and scanning electron microscopy.

3. Scorpion venom

The *Rhopalurus juncues* (also known as blue scorpion) is a type of scorpion inhabiting in Cuban island and is a member of the Buthidae family [10]. The SV has been researched for its pharmaceutical potential in clinical cancer treatments as a branch of biomedicine. Interesting enough, the venom has already been seen as a cure for cancer by the Cuban tribes long before its introduction to the modern medical field. The exposure to scorpion venom indicated cytotoxicity and selectivity against epithelial cancer cells while avoiding induction on normal cells. Quantitative analysis conducted by various researchers has shown, specifically in the MDA-MB-231 cell line at IC500.75 ± 0.15 (mg/mL), growth of breast cancer tumour cells is retarded and suppressed when the venom was administered after being extracted (via electrical stimulation) and centrifuged. Additionally, both breast cancer cell lines are two of the few most sensitive cells whose dosage between 0.1-0.75mg/ml reduced cell viability below 50% in data observed whilst other cancer cells do not perform in the same way at such low concentrations. Research has also demonstrated that primarily the pharmacodynamics of cancer treatment is via cell death associated with upregulated apoptotic genes for example Bax genes in addition to p53 (which functions through cell arrest, apoptosis). The increased expression of the Bax/BCL-2 gene proportion initiated the apoptosis pathway, incorporated Cyt c (cytochrome c) and stimulation of caspase cascades, resulting in the breakdown of substrates. Interactions with ion channels alter the cell morphology as well as volume: it was clear that malignant cells express invasive activity and grow mainly through the electrochemical ion channel efflux, for example Cl-, K+, which is induced indirectly by a rise in intracellular sodium ions as cells attempt to restore balance in early stages of apoptosis, though eventually shows reduced ion levels (from 151.5 mM total Na+/K+ concentration to 143.6 mM) [11]. Lowered total intracellular ionic strength initiates the cascade whose activity then becomes detached from its ionic strength, thus the initial decrease in the ionic strength can sustain apoptosis resulting in reduced cell size and volume [12]. Inhibitor tetrodotoxin (TTX) increases sodium and potassium ion ATPase activity and is evident to be prone to programmed cell death via apoptosis [13]. *Rhopalurus Princeps* (Rp) is also from the same genus which similarly presented inhibition of cancer cells. But more significantly, a high concentration of venom did not demonstrate cytotoxicity on normal cell lines whilst polarisation of Rp venom at extremely low concentrations exhibited great enhancement in apoptosis in BxPC3. The mechanism of action of Rp venom acts via three pathways: mitochondrial apoptosis, blockage of K, Cl channel and tissue invasion in which induction of apoptosis is the most predominant mechanism rather than inhibition of other metabolisms [5]. The venom has suggested a fascinating and advanced approach to the elimination of cancer through pharmaceutical treatments however its properties have not yet been fully unveiled.

On the other hand, breast cancer, is a member of the most numerous stimuli of relating deceases which accounts for a jarring estimated percentage of 30% of all cancers annually [2]. Despite the pre-existing treatments including chemotherapy and radiation therapy, adverse effects of these are unappealing, thus new approaches are needed to improve the efficacy and safety of such therapies. Cancer-induced pain is also a significant factor regarding the importance of pain as a prognostic symptom during the progression of the disease. BmK AGAP, *Buthus martensii* Karsch analgesic antitumoral peptide has shown astonishing properties of both analgesic and antitumor effect although the majority of the effects are unknown. Western blot, qPCR and immunofluorescence staining have all shown upregulated PTX3 expression in many cancer cell lines in breast cancer as cancer stages progress in comparison to normal breast tissues such as BT-549 in other investigated individuals.

BmK was extensively researched and studied because of its early application in human medicine in various parts of China and other Asian countries [14]. Studies demonstrated that AGAP may be

capable of specifically inhibiting Na+ ion channels as it has an inhibitor effect on the mRNA transcription of VGSC (voltage-gated sodium channel) as well as regulating malignancy of many cancer cell lines. Although VGSCs are majorly expressed in later stages of cancer development, they still occupy an essential place in controlling invasion and mobility which thus has great importance to the pharmacodynamics of therapeutic drugs such as peptides in BmK. Invasive ability and motility are greatly reduced with the induction of TTX, in which MDA-MB-231 presented noteworthy downregulation of invasion capacity in presence of inhibitor TTX, as shown in figure 4 [15].

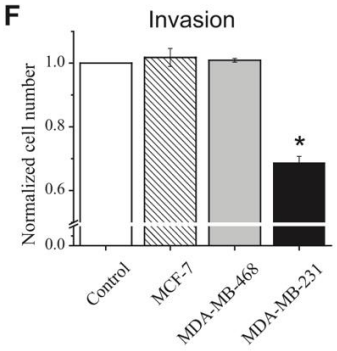

Fig. 4 At p<0.05, * TTX versus controlled situation [15].

Through sodium channel inhibition, invasive activity reduces, cells increase in volume as the concentration of Na+ rises, thus any alteration of Na+ concentration drastically results in accumulation of calcium ions, causing mass cell death via necrosis. As studies have introduced, Nav 1.5 has been discovered in both lung and breast cancer cells which are significantly expressed in comparison with the surrounding non-cancer tissue (illustrated in Fig 5) [16]. Furthermore, the overall significant expression of VGSCα in MDA-MB-231 as shown was due to Nav 1.5 which predominantly accounted for 82% of the overall VGSCα mRNA in metastatic cells while the remaining 12% is formed by Nav 1.7 (shown in Fig 6), therefore concludes a possible relation between ion channels and migration of cancers [17]. It is also worth mentioning the positive correlation between the regulation of sodium channels and the occurrence of invasive characteristics, thus new treatments could become viable through the induction of ion channel blockages.

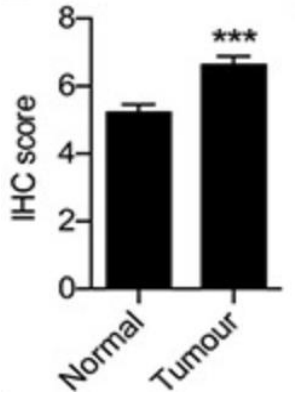

Fig. 5 Mean IHC score of normal and tumor bearing tissues [16].

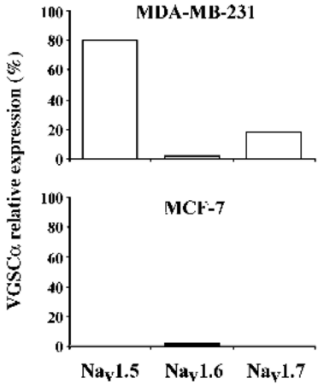

Fig. 6 Relative expression of VGSC in cell lines [17].

A study performed by Kampo et al revealed the AGAP mechanism in defeating metastasis of species as indicated in figure 9 and 10 [5]. When varying doses (1 and 0.5 mg/kg) of rBmK AGAP was injected into model animals with breast cancer, tumour growth was greatly reduced both volume-wise and weight-wise, showing the significance of both doses against cancer. As the table shows, many of scorpion venoms can induce the same effect on various types of cancer or even target the expression of the same genes. The most noticeable repetition is MCF-7 and MDA-MB-231, whose invasion ability, migration, as well as colony mitosis have been downregulated by SV from *Leiurus quinquestriatus*, *Rhopalurus junceus* and *Tityus serrulatus* etc. Despite the similarity in affected genes, there is also unavoidable variance in their mechanisms. Some are functioned by reducing expression of MMPs (matrix metalloproteinases, closely associated with cell proliferation) whilst some inducing the regulation of PTX3 (pentraxin 3) and P53, the latter often acts as a tumour suppressor to control cell division at constant rates. Studies have presented the idea that PTX3 is significantly expressed in tumours, therefore by the downregulatory effect of BmK AGAP (analgesic peptide), cancer stemness can be consequentially reduced, thus decreasing the possibility of relapses.

Table 1 different venoms and their effects on cancer cell lines [5].

Species	Venom/Peptide	Action	Target
Androctonus crassicauda	Whole venom	Inhibits proliferation of human neuroblastoma (SH-SY5Y) and human breast (MCF-7) cancer cell lines	Induces apoptosis through increasing nitric oxide production, caspase-3 activity and depolarizing mitochondrial membrane and arrests S phase
Androctonus crassicauda	Non-disulphide-bridged peptides (NDBP), AcrAPI and AcrAP2, and their high cationic analogues (HC-AcrAP) (0.001-100 uM)	HC-AcrAP analogues inhibit the proliferation of human lung adenocarcinoma (H460), breast carcinoma (MB435s) breast tumorigenic (MCF-7) and prostate carcinoma (PC-3) cell lines (IC50 2-3.6 uM)	Probably inducing cell lysis
Androctonus Bicolor Androctonus crassicauda	Whole venom (500-1000 ug/ml)	Inhibits proliferation of human breast (MDA-MB-23 I), and colorectal (HCT-8) cancer cells	Induces apoptosis more than necrotic death, and arrests cells at GO/Gl phase, upregulate p53, downregulate Bcl-xL
Androctonus	Whole venom (20-	Inhibits cell motility, and	Two mechanisms

crassicauda, Androctonus bicolor	100 ug/ml)	prevents colony mitosis of human breast, (MDA-MB-231), and colorectal (HCT-8 and HCTI16) cancer cells	proposed are i) a decrease in the expression of MMPs, and ii) a reduction in the phosphorylation levels of FAK, which is involved in cell migration and invasion.
Androctonus mauritanicus	Gonearrestide peptide (18 aa, 2192 Da) 2-200 uM	Inhibits the proliferation of human colon cancer cell line HCTI16 in dose-dependent	Arrests cancer cell cycle in Gl phase via modulating cell cycle checkpoint proteins (down-regulate CDK4, and upregulate cyclin D3, p21, p27)

(Table continued)

Species	Venom/Peptide	Action	Target
Buthus Martensil Karsch	BmK70-80kDa SVCIII (1-50 ug/ml)	Inhibits proliferation of human acute monocytic leukemia cell line (THP-I) and the human T lymphoma (Jurkat cell line) and induces cell cycle arrest at GI phase	Inhibits NF-kB activation through inhibition of Ik-Ba phosphorylation, degradation and p65 nuclear translocation
	BmK 50-60 aa 65 kDa (10-200 ug/ml)	Inhibits proliferation of DUI45 human prostate cancer cell line	Enhances expression of apoptotic gene, Bax, reduces anti-apoptotic, Bcl-2, expression, and arrests cancer cells at GI/S

Although scorpion peptides were said to have the characteristics, very little research has been conducted since the discovery. This experiment completed by S. Kampo is ground-breaking as the results have indicated that, great shrinkage in tumour size observed via sphere formation by siPTX3 as well as reduced invasive and migrative traits of both metastatic cell lines, MDA-MB-231 in addition to MCF-7 [2]. Through application of western blot, evidence has been exhibited which supports the ideology in which PTX3 expression has a great correlation with stemness, EMT (epithelial-mesenchymal transition) and potential for metastasis. When both species were treated with rBmK AGAP, it is notable that BmK has shown to have inhibiting property to cancer cell proliferation and may show a connection to cell stemness through a dose-dependent manner. Viability of both species have shown evident of almost three-fold reduction shown in Fig.7, showing an effective reduction in proliferative activities of BmK AGAP treated samples, therefore validates the direct relation between suppressed DNA replication and downregulated expression of PTX3 in breast cancer cells. As Fig 8 has illustrated, relative mRNA expressions of PTX3 decreased by nearly 50%, from 2.6 to 1.4 48h after a controlled dosage of 30 μM for both cancer cell lines, unveiling the inhibitive ability of PTX3 in cancer cells. Furthermore, rBmK AGAP also presents a tendency to inhibit migration and invasion of both metastatic cell lines at dose-dependent manner when each cell line is examined under individual assay.

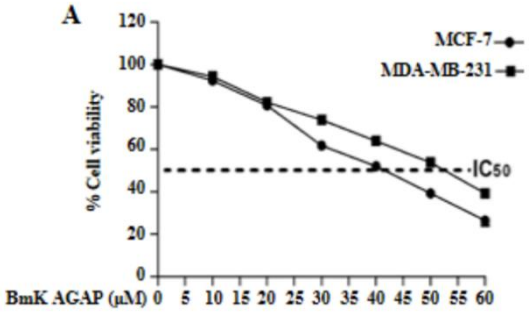

Fig. 7 Half maximal inhibitory concentrations of rBmK AGAP for different cell lines, viability treated by MTT assay [2].

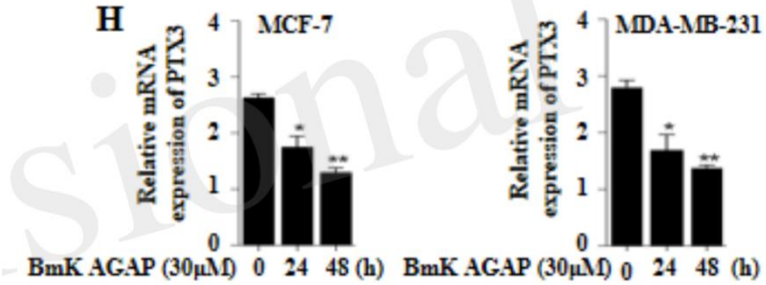

Fig. 8 Supressed PTX3 expression of different metastatic cell lines [2].

Subsequently, the effect of rBmK AGAP is also investigated in vivo through measurements of mice weights, tumour sizes and masses of tumours [2]. Treated mice have shown a decline in PTX3 levels compared to untreated, and all administration of drugs are at controlled doses of 0.5 and 1 mg/kg. Figure 9 reflects a decrease in mass of untreated mice, whilst both treated species have maintained a relatively stable weight throughout 20 days of investigation. Data shows a significant decrease in mass in untreated mice whereas treated mice show steady weight change despite reduced tumour size. Fig. 10 conveys the difference in tumour weights where mice treated with 1mg/kg has a decreased mass of 2g comparative to 2.9g in mice treated with saline (untreated), showing significant shrinkage of solid tumour. By combining both figures, it is evidently proven that tumour mass has seen remarkable declines in comparison to untreated mice although there is increase in overall body weight of both treated species. Mice treated with saline have mirrored higher percentage of tumour mass in body weight, in which reduced weight in figure 9 could be a result of continuous metastasis and invasion of such cell lines, resulting in decreased overall body mass as cancer cells develop, which unsurprisingly correlates with one of the major symptoms of cancer observed in human: weight loss. Thus, this reflects the potential of cancer treatment through the use of BmK AGAP extracted from scorpion, and further introduces prospects and potential of this cancer demolishing compound.

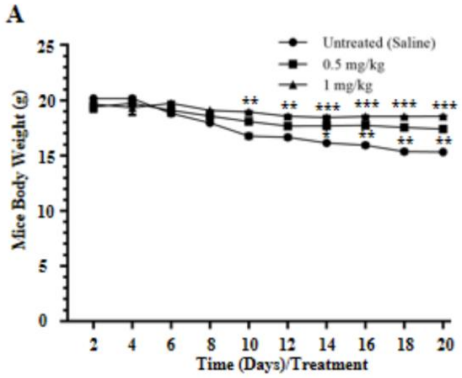

Fig. 9 Weight changes in xenograft tumors bearing and rBmK AGAP treated animal models over 20-day period [2].

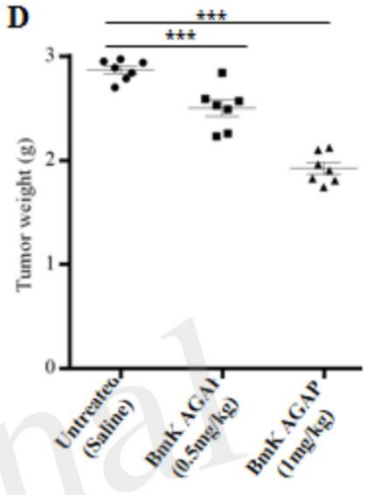

Fig. 10 Recorded mean mass change of tumor weight in treated and untreated mice [2].

4. Conclusion

In conclusion, the discovery and implementation of novel technologies enable us to learn more about the substances inside animal venom and their usages. Although no drugs composed of spider and scorpion venoms have ever been used as cancer medication historically, the development of biotoxin drugs might alter drastically if at least one of the genomes is decoded [18]. The synthesized peptide conjugation is required not only to alleviate the problem of toxin cytotoxicity but also to modify current treatments. Both scorpion peptides' characteristics, anti-cancer and analgesic abilities have huge pharmaceutical potential in clinical applications. In the future, scientists can create and modify drugs by using the research of structure-function relationships and other mechanisms. However, more work still needs to be done in the therapeutic application of components produced from animal venoms for the treatment of certain types of cancers.

References

[1] Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today. Lyon: International Agency for Research on Cancer; 2020 (https://gco.iarc.fr/today , accessed July 2022).

[2] Kampo S, Ahmmed B, Zhou T, Owusu L, Anabah TW, Doudou NR, Kuugbee ED, Cui Y, Lu Z, Yan Q, Wen QP. Scorpion Venom Analgesic Peptide, BmK AGAP Inhibits Stemness, and Epithelial-Mesenchymal Transition by Down-Regulating PTX3 in Breast Cancer. Front Oncol. 2019 Jan 25;9:21. doi: 10.3389/fonc.2019.00021. Erratum in: Front Oncol. 2021 Jun 29;11:639813. PMID: 30740360; PMCID: PMC6355678.

[3] Nyffeler M, Benz G . Spiders in natural pest control: a review . Journal of Applied Entomology, 1987, 103(1 /5): 321-339.

[4] Akef HM. Anticancer, antimicrobial, and analgesic activities of spider venoms. Toxicol Res (Camb). 2018 Mar 8;7(3):381-395. doi: 10.1039/c8tx00022k. PMID: 30090588; PMCID: PMC6060684.

[5] Mikaelian AG, Traboulay E, Zhang XM, Yeritsyan E, Pedersen PL, Ko YH, Matalka KZ. Pleiotropic Anticancer Properties of Scorpion Venom Peptides: Rhopalurus princeps Venom as an Anticancer Agent. Drug Des Devel Ther. 2020 Feb 27;14:881-893. doi: 10.2147/DDDT.S231008. PMID: 32161447; PMCID: PMC7051175.

[6] .Li F, Wu S, Chen N, Zhu J, Zhao X, Zhang P, Zeng Y, Liu Z. Fatty Acid Modification of the Anticancer Peptide LVTX-9 to Enhance Its Cytotoxicity against Malignant Melanoma Cells. Toxins (Basel). 2021 Dec 4;13(12):867. doi: 10.3390/toxins13120867. PMID: 34941705; PMCID: PMC8708390.

[7] Shen H, Xie Y, Ye S, He K, Yi L, Cui R. Spider peptide toxin lycosin-I induces apoptosis and inhibits migration of prostate cancer cells. Exp Biol Med (Maywood). 2018 May;243(8):725-735. doi: 10.1177/1535370218772802. PMID: 29763387; PMCID: PMC6378508.

[8] Tuying Yang, Yagang Zhao Research Progress on the relationship between Livin and Caspase-9 in gastric cancer [j] Journal of clinical military medicine, 2012, 40 (2): 484-487.

[9] Jian C, Zhang P, Ma J, Jian S, Zhang Q, Liu B, Liang S, Liu M, Zeng Y, Liu Z. The Roles of Fatty-Acid Modification in the Activity of the Anticancer Peptide R-Lycosin-I. Mol Pharm. 2018 Oct 1;15(10):4612-4620. doi: 10.1021/acs.molpharmaceut.8b00605. Epub 2018 Sep 17. Erratum in: Mol Pharm. 2020 Jun 1;17(6):2227. PMID: 30183307.

[10] Dioguardi M, Caloro GA, Laino L, Alovisi M, Sovereto D, Crincoli V, Aiuto R, Dioguardi A, De Lillo A, Troiano G, Lo Muzio L. Therapeutic Anticancer Uses of the Active Principles of "Rhopalurus junceus" Venom. Biomedicines. 2020 Sep 27;8(10):382. doi: 10.3390/biomedicines8100382. PMID: 32992456; PMCID: PMC7600222.

[11] Hughes FM Jr, Bortner CD, Purdy GD, Cidlowski JA. Intracellular K+ suppresses the activation of apoptosis in lymphocytes. J Biol Chem. 1997 Nov 28;272(48):30567-76. doi: 10.1074/jbc.272.48.30567. PMID: 9374553.

[12] Bortner CD, Sifre MI, Cidlowski JA. Cationic gradient reversal and cytoskeleton-independent volume regulatory pathways define an early stage of apoptosis. J Biol Chem. 2008 Mar 14;283(11):7219-29. doi: 10.1074/jbc.M707809200. Epub 2008 Jan 10. PMID: 18187415; PMCID: PMC2680553.

[13] Angus M, Ruben P. Voltage gated sodium channels in cancer and their potential mechanisms of action. Channels (Austin). 2019 Dec;13(1):400-409. doi: 10.1080/19336950.2019.1666455. PMID: 31510893; PMCID: PMC6768049.

[14] Dueñas-Cuellar RA, Santana CJC, Magalhães ACM, Pires OR Jr, Fontes W, Castro MS. Scorpion Toxins and Ion Channels: Potential Applications in Cancer Therapy. Toxins (Basel). 2020 May 15;12(5):326. doi: 10.3390/toxins12050326. PMID: 32429050; PMCID: PMC7290751.

[15] Roger, S., Besson, P., & Le Guennec, J.-Y. (2003). Involvement of a novel fast inward sodium current in the invasion capacity of a breast cancer cell line. Biochimica et Biophysica Acta (BBA) - Biomembranes, 1616(2), 107–111.doi:10.1016/j.bbamem.2003.07.001

[16] Nelson M, Yang M, Millican-Slater R, Brackenbury WJ. Nav1.5 regulates breast tumor growth and metastatic dissemination in vivo. Oncotarget. 2015 Oct 20;6(32):32914-29. doi: 10.18632/oncotarget.5441. PMID: 26452220; PMCID: PMC4741739.

[17] Fraser SP, Diss JK, Chioni AM, Mycielska ME, Pan H, Yamaci RF, Pani F, Siwy Z, Krasowska M, Grzywna Z, Brackenbury WJ, Theodorou D, Koyutürk M, Kaya H, Battaloglu E, De Bella MT, Slade MJ, Tolhurst R, Palmieri C, Jiang J, Latchman DS, Coombes RC, Djamgoz MB. Voltage-gated sodium channel expression and potentiation of human breast cancer metastasis. Clin Cancer Res. 2005 Aug 1;11(15):5381-9. doi: 10.1158/1078-0432.CCR-05-0327. Erratum in: Clin Cancer Res. 2005 Nov 15;11(22):8224. PMID: 16061851.

[18] Wu T, Wang M, Wu W, Luo Q, Jiang L, Tao H, Deng M. Spider venom peptides as potential drug candidates due to their anticancer and antinociceptive activities. J Venom Anim Toxins Incl Trop Dis. 2019 Jun 3;25:e146318. doi: 10.1590/1678-9199-JVATITD-14-63-18. PMID: 31210759; PMCID: PMC6551028.